

Amendments to the Drawings

The attached sheets of drawings includes changes to Figure 2 and Figure 4.

These sheets replace the original sheets. In Figure 2, the designation of 2A and 2B has been added. Figure 4 is being resubmitted for clarity purposes.

Attachment: Replacement Sheets
Annotated Sheets Showing Changes

Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-8, 11, 15, 16, 26, 40-42, 45, 49 and 70-75 are pending in the application, with claim 1 being the independent claim. Claims 9, 10, 12-14, 17-25, 27-39, 43, 44, 46-48, 50-69 and 76-81 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 1, 2, 4, 5, 11, 15, 16, 26, 40, 41, 45, 49 and 70-74 are sought to be amended. Support for the amendment to claim 1 may be found in the specification as filed, *e.g.*, Examples 2, 3, and 5; Figure 4 and Figure 6. The amendments to claims 2, 4, 5, 11, 15, 16, 26, 40, 41, 45, 49 and 70-74 are sought to correct antecedent basis. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Summary of the Office Action

In the Office Action dated August 11, 2009, the Examiner has made two objections to the specification, one objection to the drawings, one objection to the claims, and six rejections of the claims. Applicants respectfully offer the following remarks concerning these objections and rejections.

III. Objection to the Specification

At page 4 of the Office Action, the Examiner has objected to the specification for two typographical errors. The specification has been amended to correct the typographical errors. Thus, Applicants respectfully assert that the objection has been overcome. Accordingly, Applicants respectfully request that the objection be reconsidered and withdrawn.

IV. Objections to the Drawings

At pages 4-5 of the Office Action, the Examiner has objected to Figure 2 for allegedly failing to comply with 37 C.F.R. § 1.84(p)(5) because Figure 2 does not include a reference sign mentioned in the description. Applicants submit two sheets of formal replacement drawings in order to comply with 37 C.F.R. § 1.84(p)(5). Identification of the replacement drawing sheet submitted herewith is provided in accordance with 37 C.F.R. §§ 1.84(c) and 1.121(d). Acknowledgement of the receipt, approval, and entry of the replacement drawing sheets into this application is respectfully requested.

V. Objections to the Claims

At page 5 of the Office Action, the Examiner has objected to claims 1-9, 15, 16, 40-42, 45, 49 and 70-75 for allegedly comprising non-elected subject matter. Applicants have amended these claims to remove the non-elected subject matter. Thus, Applicants respectfully assert that the objection has been overcome. Accordingly, Applicants respectfully request that the objection be reconsidered and withdrawn.

VI. *Obviousness-Type Double-Patenting Rejection*

A. *Claims 1-5, 40-42 and 49*

At pages 6-7 of the Office Action, the Examiner has rejected claims 1-5, 40-42 and 49 under the judicially created doctrine of obviousness type double-patenting over claims 3-7 of U.S. Appl. No. 11/547,871. Applicants respectfully request that this rejection be held in abeyance until subject matter that is otherwise allowable is identified, at which time Applicants will consider filing a terminal disclaimer to obviate this rejection.

B. *Claims 1-6, 8-11, 15, 16, 26, 45 and 49*

At pages 7-9 of the Office Action, the Examiner has rejected claims 1-6, 8-11, 15, 16, 26, 45 and 49 under the judicially created doctrine of obviousness type double-patenting over claims 3, 17, 21-24, 26-32, 47, 55, 57-62, 64-69 and 70 of U.S. Appl. No. 10/594,188. Applicants respectfully request that this rejection be held in abeyance until subject matter that is otherwise allowable is identified, at which time Applicants will consider filing a terminal disclaimer to obviate this rejection.

VII. *The Rejections Under 35 U.S.C. § 102(b) are Traversed*

A. *Muller*

At pages 9-12 of the Office Action, the Examiner rejected claims 1, 2, 4, 5, 7-16, 26, 40, 41, 45, 49 and 70-73 for allegedly being anticipated by Muller *et al.*, *FASEB J* 14:2540-2548 (2000) (hereinafter "Muller"). Applicants respectfully traverse this rejection.

Present claim 1 (and thus the claims depending therefrom) is drawn to a method of modeling or obtaining cardiac tissue or tissue-like structures comprising (a) culturing

embryonic stem (ES) cell-derived differentiating or differentiated cardiomyocytes in the presence of differentiating or differentiated fibroblasts and differentiating or differentiated endothelial cells; and (b) allowing integration and alignment of said differentiating or differentiated cardiomyocytes, fibroblasts and endothelial cells into cardiac tissue or tissue-like structures; wherein said differentiating or differentiated cardiomyocytes acquire longitudinal morphology upon integration and alignment with fibroblasts and endothelial cells; and wherein said cardiac tissue or tissue-like structures exhibit contractility and cross striation.

In contrast, Muller only discloses a method of culturing mouse embryonic stem cells to form cardiomyocytes. Muller does not disclose a method of obtaining cardiac tissue or tissue like structures by culturing differentiating or differentiated cardiomyocytes with differentiating or differentiated fibroblasts and endothelial cells and allowing the integration and alignment of the cardiomyocytes with the fibroblasts and endothelial cells, wherein the cardiomyocytes acquire longitudinal morphology upon integration and alignment with the fibroblasts and endothelial cells; and wherein the cardiac tissue or tissue-like structures exhibit contractility and cross striation, as required by the present claims.

The Examiner asserts that while "Muller focuses on cardiomyocytes produced by EB formation, Muller acknowledges that this method results in spontaneous differentiation into a variety of cell lineages including endothelial cells and fibroblast cell[s]." *See* Office Action at page 11. Thus, the Examiner concludes that "inherently the EB formation results in a coculture and alignment of multiple cell type . . . in the EB culture." *See* Office Action at page 11. Applicants respectfully disagree with the Examiner's contentions and conclusion. First, despite the Examiner's assertion to the

contrary, Muller does not disclose fibroblasts. In addition, while Muller discloses that embryonic stem cells can be induced to differentiate into multiple cell types, Muller does not indicate that there are multiple cell types, *e.g.*, cardiomyocytes, fibroblasts, and endothelial cells in the cell culture disclosed in the reference. Furthermore, Muller does not disclose that cardiomyocytes acquire longitudinal morphology upon integration and alignment with the fibroblasts and endothelial cells. To rely on an inherency argument, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (PTO Bd. Pat. App. Int. 1990) (emphasis in original). This burden has not been met in the present case, since there is no disclosure in Muller that EB formation "necessarily" results in a co-culture and integration and alignment of cardiomyocytes, fibroblasts and endothelial cells.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). As discussed above, Muller does not expressly or inherently disclose every element of the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b). In view of the foregoing remarks, Applicants respectfully assert that Muller does not anticipate the currently presented claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Muller therefore are respectfully requested.

B. Franz

At pages 12-13 of the Office Action, the Examiner rejected claims 1, 2, 3-5, 7-16, 26, 40, 41, 45, 49 and 70-74 for allegedly being anticipated by Franz (U.S. Patent No. 5,928,943 (hereinafter "Franz")). Applicants respectfully traverse this rejection.

As discussed above, present claim 1 (and thus the claims depending therefrom) is drawn to a method of modeling or obtaining cardiac tissue or tissue-like structures comprising (a) culturing embryonic stem (ES) cell-derived differentiating or differentiated cardiomyocytes in the presence of differentiating or differentiated fibroblasts and differentiating or differentiated endothelial cells; and (b) allowing integration and alignment of said differentiating or differentiated cardiomyocytes, fibroblasts and endothelial cells into cardiac tissue or tissue-like structures; wherein said differentiating or differentiated cardiomyocytes acquire longitudinal morphology upon integration and alignment with the fibroblasts and endothelial cells; and wherein said cardiac tissue or tissue-like structures exhibit contractility and cross striation.

In contrast, Franz is only directed toward the generation of cardiac muscle cells. Franz does not disclose a method of obtaining cardiac tissue or tissue like structures by culturing differentiating or differentiated cardiomyocytes with differentiating or differentiated fibroblasts and endothelial cells and allowing the integration and alignment of the cardiomyocytes with the fibroblasts and endothelial cells, wherein the cardiomyocytes acquire longitudinal morphology upon integration and alignment with the fibroblasts and endothelial cells; and wherein the cardiac tissue or tissue-like structures exhibit contractility and cross striation, as required by the present claims.

As discussed above, under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art

reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). As discussed above, Franz does not expressly or inherently disclose every element of the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b). In view of the foregoing remarks, Applicants respectfully assert that Franz does not anticipate the currently presented claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Franz therefore are respectfully requested.

VIII. The Rejection Under 35 U.S.C. § 103(a) is Traversed

At pages 13-16 of the Office Action, the Examiner has rejected claims 1, 3, 6, 42 and 75 for allegedly being obvious over Franz in further view of Wantanabe *et al.*, *Biochem. Biophys. Res. Com.* 213:130-137 (1995) (hereinafter "Wantanabe"), Muller and Feld *et al.*, *Circulation* 105:522-529 (2002) (hereinafter "Feld"). Applicants respectfully disagree with this rejection.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 745 F.2d 1468, 1471-73 (Fed. Cir. 1984). As set forth in *Graham v. John Deere Co. of Kansas City*, "[u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." 383 U.S. 1, 17 (1966). This has been the standard for over 40 years, and remains the law today. *See KSR Int'l. Co. v. Teleflex Inc.*, No. 04-1350, slip op. (2007). If, after these

criteria are considered, the evidence indicates that the claimed invention is obvious over the prior art, it may be said that a *prima facie* case of obviousness have been established.

The Office has published Examination Guidelines to aid Examiners in formulating obviousness rejections. *See* MPEP § 2141 (hereinafter "the Examination Guidelines"). Seven rationales are suggested by which obviousness may be found, *e.g.*, by combining elements in the art or substituting one known element for another. As a common thread through all the rationales, the Examiner must establish on the record that a person of ordinary skill in the art would have recognized that the results of the combination or substitution were *predictable*. *Id.*, *e.g.*, at 57529.

The Examiner has not met the burden of establishing a *prima facie* case of obviousness based on the Examination Guidelines. Specifically, the Examiner has not established that the ordinary artisan reading Franz in view of Wantanabe, Muller and Feld would have predictably arrived at the presently claimed method of obtaining cardiac tissue or tissue-like structures.

The present invention provides for a method of obtaining cardiac tissue or tissue-like structures by culturing differentiating or differentiated cardiomyocytes in the presence of differentiating or differentiated fibroblasts and differentiating or differentiated endothelial cells. *See* specification at Examples 2 and 5. Specifically, as shown in Figure 4, the cardiomyocytes tightly integrate and align with the fibroblasts and acquire a longitudinal morphology and orientation with the surrounding fibroblasts. *See* Figure 4 (attached in appendix) and specification at Examples 2 and 5. As discussed in the specification, the cardiomyocyte-fibroblast interaction is a basic structural feature of heart tissue (wherein the fibroblasts even outnumber the number of cardiomyocytes) and is a key to functional integration of the multitude of cardiac cells into one contractile

organ. Furthermore, endothelial cells play an important role as a trophic element for cardiomyocytes because of their capillary and vessel-forming ability. *See* specification at Example 5. This is an important aspect of the invention as a whole. The formation of the cardiac tissue or tissue-like structures results from the culturing of the cardiomyocytes, fibroblasts and endothelial cells together. In contrast, the art cited by the Examiner would not have provided a reasonable expectation of success in obtaining the presently claimed method because the mere substitution or combination of elements from the combination of references cited by the Examiner would not have resulted in the production of cardiac tissue or tissue-like structures, as presently claimed.

As discussed above, Franz is directed toward the generation of cardiac muscle cells and Muller is directed towards a method of culturing mouse embryonic stem cells to form cardiomyocytes. Neither Franz nor Muller teach or suggest a method of obtaining cardiac tissue or tissue-like structures by culturing differentiating or differentiated cardiomyocytes in the presence of differentiating or differentiated fibroblasts and endothelial cells. Thus, one of ordinary skill in the art would not have predicted a method to obtain cardiac tissue or tissue-like structures based on Franz or Muller.

In addition, neither Wantanabe nor Feld suggest culturing differentiating or differentiated cardiomyocytes in the presence of differentiating or differentiated fibroblasts and endothelial cells to form cardiac tissue or tissue-like structures. While Feld discloses that fibroblasts transfected with a voltage-gated potassium channel are able to modify the electrophysiological properties of cardiomyocytic cultures, Feld does not teach or suggest culturing differentiating or differentiated fibroblasts that have not been transfected with a voltage-gated potassium channel with cardiomyocytes and endothelial cells in order to form cardiac tissue or tissue-like structures. *See* Feld at page

522, right column. Thus, one of ordinary skill in the art would not have predicted a method to obtain cardiac tissue or tissue-like structures based on Feld or Wantanabe.

Accordingly, the ordinary artisan reading the combination of references cannot predictably arrive at the presently claimed invention of obtaining cardiac tissue or tissue-like structures by culturing differentiating or differentiated cardiomyocytes in the presence of differentiating or differentiated fibroblasts and differentiating or differentiated endothelial cells and allowing the integration and alignment of cardiomyocytes with the fibroblasts and endothelial cells, wherein the cardiomyocytes acquire longitudinal morphology upon integration and alignment with the fibroblasts and endothelial cells; and wherein the cardiac tissue or tissue-like structures exhibit contractility and cross striation. Specifically, the references do not disclose the element of culturing differentiating or differentiated cardiomyocytes in the presence of differentiating or differentiated fibroblasts and endothelial cells in order to obtain the cardiac tissue or tissue-like structures. Therefore, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness and respectfully request that this rejection be withdrawn.

IX. The Rejections Under 35 U.S.C. § 112, Second Paragraph are Traversed

A. Claims 1-16, 26, 40-42, 45, 49 and 70-75

At page 17 of the Office Action, the Examiner has rejected claims 1-16, 26, 40-42, 45, 49 and 70-75 for allegedly being indefinite for reciting "a tissue-like structure." Applicants respectfully disagree. However, in order to further prosecution, Applicants have amended claim 1 to recite that the "cardiac tissue or tissue-like structures exhibit contractility and cross striation." Thus, Applicants respectfully assert that one of

ordinary skill in the art would understand that a "tissue-like structure" would have to possess certain structural properties. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

B. *Claims 40-42*

At page 17 of the Office Action, the Examiner has rejected claims 40-42 for allegedly not having sufficient antecedent basis. Applicants have amended claim 40 to recite "analyzing the physiological or developmental status or both of the cardiomyocytes and fibroblasts." Thus, Applicants believe this rejection has been overcome. Reconsideration and withdrawal of the rejection are respectfully requested.

C. *Claim 73*

At page 17 of the Office Action, the Examiner has rejected claim 73 for allegedly not having sufficient antecedent basis. Applicants have amended claim 73 to recite "[t]he method of claim 72." Thus, Applicants believe this rejection has been overcome. Reconsideration and withdrawal of the rejection are respectfully requested.

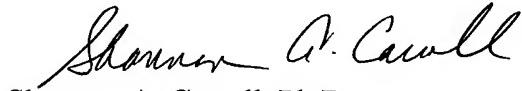
X. *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Shannon A. Carroll, Ph.D.
Attorney for Applicants
Registration No. 58,240

Date: November 12, 2009

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

1041257_1.DOC